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(57) Abstract

Compositions are provided, which contain an orally active cephalosporin antibiotic and an agent capable of reducing under wet conditions intrinsically sticking properties of the active ingredient. The compositions, which may contain a high amount of active ingredient, on oral administration show an acceptable intra– and interindividual variation in bioavailability profiles.

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# ORAL COMPOSITIONS CONTAINING A CEPHALOSPORIN ANTIBIOTIC

The present invention relates to compositions containing an orally active cephalosporin antibiotic.

## BACKGROUND OF THE INVENTION

Orally absorbed cephalosporins have been in clinical use for almost thirty years. The cephalosporins, belonging to the group of the beta-lactam antibiotics, are bactericidal and, similarly to the penicillins, they act by inhibiting the bacterial cell wall. The cephalosporins are classified by generation, which is primarily based on the general features of their antibacterial activity. Succeeding generations generally have increasing activity against Gram-negative bacteria. Although the number of available oral agents is increasing, it is still small in comparison with the injectable cephalosporins. Examples of currently marketed orally active cephalosporins are cefuroxime axetil, cefixime trihydrate, cefadroxil, cefpodoxime proxetil, cefatrizine, ceftibuten, cefalexin, cephradine and cefaclor. It is interesting to note that these compounds belong to different generations. It will therefore readily be recognised that due to the relative scarcity of these compounds it is important to further explore the possibilities to improve dosage-forms containing such antibiotics. E.g. cefaclor, a second generation product, has been marketed in the United States of America since 1979. It still is a widely used broad spectrum antibiotic having a good activity after oral administration both against Gram-positive cocci and Gram-negative bacteria. It is primarily used in the treatment of upper and lower respiratory tract infections, but urinary tract, skin and soft tissue infections have also been successfully treated with the compound. In view of its activity against Haemophilus influenzae it is very suitable for the treatment of infections such as otitis media. Due to the short serum elimination half life of $\leq$ 1 hour, the usual adult dose for cefaclor is 250 to 500 mg every 8 hours. For current therapeutic practice cefaclor is commercially available as a capsule, modified release tablet, suspension and more recently as a dispersible tablet. The commercial availability of such different dosage-forms reflects the prescriber's need to select the most appropriate dosage-form for each individual patient.

On oral administration of the above-mentioned cephalosporins bioavailability problems may be encountered. For cefuroxime axetil an erratic absorption was reported from tablets and the absorption is said to be enhanced in the presence of food. Cefixime trihydrate shows a slow absorption which is independent from food intake. However absorption is not complete (40-50%) and appears to be influenced by the dosage-form from which it is released: better bioavailability profiles are achieved from a suspension than from a tablet formulation. Cefpodoxime proxetil shows an absorption of only 50% in fasting subjects, whilst the absorption is increased in the presence of food. However, absorption decreases under conditions of low gastric acidity and also with the concurrent administration of antacids. Cefalexin, cephradine and cefaclor are generally well-absorbed. Absorption may be delayed by food, but is essentially not altered by it. However, according to current standards e.g. cefaclor is considered to provide intra- and interindividual differences in bioavailability profiles. In particular the peak serum concentration and time to peak serum concentration may be effected. In addition thereto according to Japanese patent application 5-150628 cefaclor is slowly soluble at a relatively low pH and, since it is absorbed in the upper part of the small intestine only, a relatively small portion may become available for absorption. On dissolving cefaclor in a medium, which has a relatively high pH, the bioavailability however decreases.

The above problems encountered with orally active cephalosporins call for a new approach in formulation design in order to increase their applicability in the treatment of infections and at the same time to avoid the use of injectable cephalosporins.

A technique for obtaining oral formulations, which is generally applicable to different drugs, having a solubility in water of less than 10%, is disclosed in EP-0330284-B. The drug is blended with 20-100 wt% of a cellulose product, which is microcrystalline cellulose, microfine cellulose or a mixture thereof, and granulated with an aqueous solution, containing up to 0.5 wt% of a wet granulation binding agent, all percentages based on the weight of the active ingredient. After drying and sieving the granules these may be blended with suitable excipients, such as disintegrants, lubricants and flavours. A specific example thereof is disclosed in EP-0281200-B, which describes fast-disintegrating tablets, containing an amphoteric beta-lactam antibiotic. Disintegration times of these tablets were reported to be within one minute in general. The bioavailability

of the active ingredient was demonstrated to be independent of the way of taking the medicine. However, the amount of active ingredient that could be incorporated in the tablets appeared to be relatively limited.

A dispersible tablet formulation specifically designed for cefaclor, which tablet disintegrates within 3 minutes in water of room temperature, was recently disclosed in EP-0716852. These tablets are prepared by direct compression techniques and do not contain more than 50 wt% of the active ingredient.

Not only from a patient compliance point of view but also from an economic and environmental point of view there is a need to use only minimal amounts of excipients in oral drug dosage-forms.

The problem to be solved by the present invention thus was to provide a composition, which contains a high amount of a cephalosporin antibiotic and which on oral administration shows an acceptable intra- and interindividual variation in bioavailability of the active ingredient.

## SUMMARY OF THE INVENTION

The object of the present invention is to provide compositions for oral administration comprising a cephalosporin antibiotic and an agent capable of reducing under wet conditions intrinsically sticking properties of the said antibiotic, optionally in admixture with pharmaceutically acceptable excipients.

It is another object of the present invention to provide use of an agent, selected from the group consisting of sodium lauryl sulfate, cross-linked polyvinylpyrrolidone, sodium starch glycolate, bentonite, magnesium aluminium silicate, croscarmellose sodium and microcrystalline cellulose, in a composition for oral administration, containing a cephalosporin antibiotic, for reducing under wet conditions intrinsically sticking properties of the said antibiotic.

## DETAILED DESCRIPTION OF THE INVENTION

It has now been found that the addition of certain inert agents, well-known as pharmaceutically acceptable excipients for incorporation into dosage-forms, can markedly reduce under wet conditions intrinsically sticking properties of a cephalosporin antibiotic. Surprisingly the compounds, which have appeared to be useful in this respect, do not necessarily belong to a certain class of compounds, which are related with respect to their chemical structure or with respect to their generally recognised functional properties: sodium lauryl sulfate, cross-linked polyvinylpyrrolidone, sodium starch glycolate, bentonite, magnesium aluminium silicate, croscarmellose sodium and microcrystalline cellulose.

Sodium lauryl sulfate consists of a mixture of sodium alkyl (mainly lauryl) sulfates with residual quantities of sodium chloride and sodium sulfate. Due to its surface-active properties it finds ample use as an (anionic) emulsifying or solubilising agent.

Cross-linked polyvinylpyrrolidone is a water insoluble fine powder, which is advantageously used as a tablet disintegrant.

Sodium starch glycolate or sodium carboxymethyl starch is a synthetically prepared tablet and capsule disintegrant, occurring as oval or spherical granules of micrometer size.

Bentonite and magnesium aluminium silicate are crystalline, clay-like minerals. Both are colloidal, hydrated aluminium silicates. The difference between bentonite and magnesium aluminium silicate is the higher rate of substitution of magnesium for aluminium in the latter. The application of both materials in pharmaceutical preparations is both similar and manifold, the most well-known use being as a suspending and/or viscosity increasing agent.

Croscarmellose sodium or cross-linked sodium carboxymethyl cellulose is a free-flowing, water insoluble powder, that can strongly adsorb to other materials. Since it has a high affinity for water it is widely used as a disintegrant.

Microcrystalline cellulose is a purified, partially depolymerised alpha-cellulose, occurring as a crystalline powder composed of porous particles. It is widely used as a tablet and capsule diluent and tablet disintegrant.

In particular for microcrystalline cellulose it has been demonstrated that it can be advantageously used for the purpose as mentioned above.

The agent capable of reducing the under wet conditions intrinsically sticking properties of the cephalosporin antibiotic can be used in an amount of up to 17 wt%, the percentage based on the weight of the antibiotic compound. Preferred concentrations to be used depend on the choice of the agent(s). Sodium lauryl sulfate, cross-linked polyvinylpyrrolidone, sodium starch glycolate, bentonite, magnesium aluminium silicate and croscarmellose sodium may be added in such low amounts of 0.1-3 wt%. For microcrystalline cellulose a concentration of up to 17 wt%, but preferably 1-10 wt% and most preferably 5-9 wt% is used. If deemed necessary lower amounts can also be used. Although the addition of the said agent to the antibiotic compound has appeared to be essential to avoid any intrinsic stickiness of the active compound in an aqueous solution, especially on placing the same in an aqueous liquid having a low pH and at 37°C, surprisingly the concentration thereof can be kept low. Accordingly the cephalosporin antibiotic can be present in the composition in an amount of more than 83 wt%. Also mixtures of the above-mentioned agents can be used advantageously.

The compositions according to the present invention can be prepared in several ways. One of the methods comprises the preparation of a granulate by wet granulation techniques. Such granulate is prepared by dry blending of the cephalosporin antibiotic and the agent capable of reducing the under wet conditions intrinsically sticking properties of the antibiotic compound, moistening the mixture with an aqueous solution which may contain up to 0.5 wt% of a wet granulation binding agent, screening the mass through a first sieve, drying it in a fluid bed dryer, and screening the granules through a second sieve. A granulate can also be prepared by moistening the active ingredient with an aqueous liquid, containing the agent in a dissolved or suspended form, screening the mass through a first sieve, drying it in a fluid bed dryer and screening the granules through a second sieve. In case a mixture of agents, capable of reducing the under wet conditions intrinsically sticking properties of the cephalosporin antibiotic, is used, these agents can all be incorporated into the granulate or located outside the granulate or one of the agents can be put into the granulate and the other one(s) outside the granulate.

The granulating liquid may optionally contain a wet granulation binding agent. Concentrations of up to 0.5 wt%, preferably 0.1 wt%, the percentages based on the weight of

the active ingredient, may be used without adversely effecting the disintegrating and dissolving properties of the dosage-form. Examples of wet granulation binding agents include soluble cellulose compounds, such as methyl cellulose, natural gums (acacia, guar), gelatin, polyvinylpyrrolidones, starches etc.

The amount of aqueous granulation liquid may vary between 15 and 50 wt%, preferably 20 and 40 wt% and more preferably 25 and 35 wt%, the percentages based on the weight of the granulate, without effecting the fast-disintegrating and fast-dissolving properties of the compositions according to the present invention.

Examples of disintegrants which can be advantageously used to obtain fast-disintegrating tablets are cross-linked polyvinylpyrrolidone, low-substituted hydroxypropyl cellulose, sodium starch glycolate, an ion-exchange resin, such as polacrilin potassium (Amberlite IRP 88®) and microcrystalline cellulose.

Since it is of utmost importance to avoid any stickiness in a medium or body liquid having a low pH, which would adversely effect the bioavailability of the cephalosporin antibiotic, preferred disintegrants are cross-linked polyvinylpyrrolidone and low-substituted hydroxypropyl cellulose. Fast disintegration times of tablets, containing a high amount of active ingredient, can be obtained using the above-mentioned disintegrants in a preferred amount of between 1.5 and 7.5 wt%, more preferably between 2.2 and 5.0 wt%, the percentages based on the weight of the composition. The addition of an extragranular disintegrant may be optional.

By fast disintegration is meant a disintegration time in water of room temperature (20°C) of less than two minutes and preferably less than one minute. For the assessment thereof the method according to the European Pharmacopoeia is used. The same method, wherein the movement of the arm, carrying the disintegration basket, is limited to 22 mm instead of 55 mm, is used for simulating a user's situation.

Fast-dissolution is to be considered as >95% of the drug dissolved in a suitable dissolution medium, e.g. as prescribed in the U.S. Pharmacopoeia XXIII for each particular drug, of 37°C, after 30 minutes. Preferably 90% of the drug has been dissolved after 10 minutes (same conditions).

The compositions according to the present invention show many advantages. In a bioequivalence study a cefaclor-containing tablet according to the present invention, either taken as such or after prior dispersal in water, has proved to be equivalent to commercially available compositions. Furthermore, the considerable variation in inter- and intra-individual bioavailability profiles was observed to be reduced.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be readily apparent to those of ordinary skill in the art in the light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit and the scope of the appended claims.

The following examples further illustrate the invention.

# EXAMPLES

## Example 1

919.3 g of cefaclor and 80.7 g of microcrystalline cellulose (Avicel® PH 102) were mixed in a planetary mixer during 5 minutes. Thereafter 350 g of water were gradually added to the powder mixture while mixing was continued for another 15 minutes. The wet mass was screened using a 2 mm sieve and subsequently dried in a Retsch fluid bed dryer at an air inlet temperature of 50°C. The dried granulate was screened through a 1.0 mm sieve.

## Example 2

| | |
|---|---|
| Granulate of example 1 | 912.00 g |
| sodium starch glycolate | 42.88 g |
| flavours | 16.00 g |
| saccharinic acid | 14.40 g |
| colloidal silicon dioxide | 2.56 g |
| magnesium stearate | 12.16 g |

## Example 3

| | |
|---|---|
| cefaclor monohydrate | 524 mg |
| microcrystalline cellulose | 46 mg |
| cross-linked polyvinylpyrrolidone | 30 mg |
| flavours | 10 mg |
| saccharinic acid | 9 mg |
| magnesium stearate | 5 mg |

Cefaclor monohydrate was mixed with the intragranular excipient and granulated in a high speed mixer (rotor speed 1000 tpm) with 25 wt% of water during 5 minutes. The wet mass was dried in a fluid bed dryer and thereafter sieved using an oscillating granulator equipped with a 1 mm screen and a 630 µm screen respectively. The granules so obtained were blended with the remaining excipients and compressed to tablets, having a mean weight of about 625-650 mg and a hardness of 6.3 kP, on a single punch press using 17.5 x 9 mm oval tooling.

| dissolved amount of cefaclor (%) | time (min) |
|---|---|
| 89.3 | 4 |
| 94.4 | 6 |
| 96.0 | 8 |
| 96.3 | 10 |
| 97.9 | 20 |
| 98.9 | 30 |

Example 4

Tablets, having the composition as shown in the tables below, were prepared according to the method described in example 3. The characteristics of the tablets thus obtained are shown in the table.

| | |
|---|---|
| cefaclor monohydrate | 524 mg |
| microcrystalline cellulose | 46 mg |
| disintegrant (see the table below) | 30 mg |
| flavours | 19 mg |
| lubricant | 5 mg |

| Disintegrant | Hardness (kP) | Friability (%) | Disintegration time according to Ph.Eur. method (s) | Disintegration time according to users' test (s) |
|---|---|---|---|---|
| polacrilin potassium | 6.9 | 0.0 | 46.0 | 67.7 |
| cross-linked polyvinylpyrrolidone | 6.3 | 0.0 | 20.2 | 24.7 |
| low-substituted hydroxypropyl cellulose | 7.0 | 0.0 | 26.7 | 37.7 |
| sodium starch glycolate | 6.9 | 0.0 | 31.5 | 48.7 |
| microcrystalline cellulose | 6.8 | 0.0 | 22.0 | 30.2 |

Example 5

A granulate and tablets, were prepared according to the method described in example 3. The quantitative composition of the granulate as well as the hardness of the tablets were varied as shown in the table herebelow.

| Amount of cefaclor (wt%)* | Amount of microcrystalline cellulose (wt%)* | Hardness (kP) | Friability (%) | Disintegration time according to Ph.Eur. (s) | Disintegration time according to users' test (s) |
|---|---|---|---|---|---|
| 84 | 7.37 | 7.1 | 0.0 | 16.7 | 24.0 |
| 84 | 7.37 | 11.2 | 0.0 | 20.3 | 29.3 |
| 84 | 7.37 | 16.1 | 0.0 | 55.7 | 55.8 |
| 86.47 | 4.6 | 7.0 | 0.0 | 16.0 | 23.7 |
| 86.47 | 4.6 | 11.6 | 0.0 | 21.7 | 32.8 |
| 89.1 | 1.7 | 6.8 | 0.0 | 16.8 | 25.7 |
| 89.1 | 1.7 | 12.1 | 0.0 | 30.8 | 36.5 |

*: percentage based on the weight of the composition

Example 6

300 g of cefaclor were granulated with 105 ml of an aqueous liquid containing 2 wt% of magnesium aluminium silicate according to the method described in example 1. After blending the granulate with the excipients as mentioned in the table herebelow, tablets weighing between 310-315 mg and having a hardness of between 4.0 and 5.3 kP were compressed. The disintegration time in water was < 1 minute.

| | composition I | composition II | composition III |
|---|---|---|---|
| granulate | 263.8 g | 263.8 g | 263.8 g |
| microcrystalline cellulose | 44.0 g | 22.0 g | - |
| l-HPC | - | 22.0 g | 44.0 g |
| colloidal silicon dioxide | 0.8 g | 0.8 g | 0.8 g |
| magnesium stearate | 3.8 g | 3.8 g | 3.8 g |

Example 7

300 g of cefaclor were granulated with 105 ml of an aqueous liquid containing 2 wt% of cross-linked polyvinylpyrrolidone according to the method described in example 1. After blending the granulate with the excipients as mentioned in the table herebelow tablets having a mean weight of 325 mg were compressed. The disintegration time of the tablets in water was < 1 minute.

| | |
|---|---|
| granulate | 263.8 g |
| microcrystalline cellulose | 44.0 g |
| colloidal silicon dioxide | 0.8 g |
| magnesium stearate | 3.8 g |

Example 8

293 g of cefaclor were blended with 7 g of bentonite. The mixture was granulated with 105 ml of water according to the method described in example 1. The granulate after mixing with the excipients mentioned herebelow was compressed into tablets of about 300 mg. The disintegration time in water was < 1 minute.

| | composition I | composition II |
|---|---|---|
| granulate | 268.2 | 268.2 |
| microcrystalline cellulose | 22.0 | - |
| l-HPC | 22.0 | 44.0 |
| colloidal silicon dioxide | 0.8 | 0.8 |
| magnesium stearate | 3.8 | 3.8 |

## Example 9

524 g of cefaclor were blended with 12.5 g of sodium starch glycolate and thereafter granulated with water according to the method of example 1. After mixing the granulate with the excipients as indicated in the table herebelow tablets having a weight of between 310-320 mg and a hardness of between 4.0 and 4.5 kP were compressed. The disintegration time was < 1 minute.

| | composition I | composition II | composition III |
|---|---|---|---|
| granulate | 268.2 | 268.2 | 268.2 |
| microcrystalline cellulose | 40.0 | 20.0 | - |
| l-HPC | - | 20.0 | 40.0 |
| colloidal silicon dioxide | 0.8 | 0.8 | 0.8 |
| magnesium stearate | 3.8 | 3.8 | 3.8 |

## Example 10

300 g of cefaclor were granulated with 75 ml of an aqueous liquid, containing 1.4 g of sodium lauryl sulfate according to the method of example 1. After blending the granulate with the excipients mentioned herebelow, tablets having a weight of between 300 and 325 mg and a hardness of between 3.5 and 4.8 kP were compressed. The disintegration time was < 1 minute.

| | composition I | composition II |
|---|---|---|
| granulate | 263.2 | 263.2 |
| microcrystalline cellulose | 22.0 | - |
| l-HPC | 22.0 | 44.0 |
| colloidal silicon dioxide | 0.8 | 0.8 |
| magnesium stearate | 3.8 | 3.8 |

Example 11

| | |
|---|---|
| cefaclor monohydrate | 262.0 g |
| croscarmellose sodium | 2.1 g |
| microcrystalline cellulose | 44.0 g |
| colloidal silicon dioxide | 0.8 g |
| magnesium stearate | 3.8 g |

100 g of cefaclor were granulated with 40 ml of an aqueous liquid containing 0.8 g of croscarmellose sodium according to the method of example 1. After blending the granulate with the remaining excipients tablets having a mean weight of 319 mg and a hardness of 4.4 kP were compressed. The disintegration time of the tablets in water was 60 s.

Example 12

| | |
|---|---|
| cefaclor monohydrate | 262.0 g |
| microcrystalline cellulose | 23.0 g |
| l-HPC | 23.0 g |
| colloidal silicon dioxide | 0.8 g |
| magnesium stearate | 3.8 g |

100 g of cefaclor were granulated with 25 ml of water according to the method described in example 1. After blending the granulate with the remaining excipients tablets having a mean weight of 322 mg and a hardness of 4.9 kP were compressed. The disintegration time in water was 26.5 s.

Example 13

| | |
|---|---|
| cefaclor monohydrate | 262.0 g |
| microcrystalline cellulose | 34.5 g |
| l-HPC | 11.5 g |
| colloidal silicon dioxide | 0.8 g |
| magnesium stearate | 3.8 g |

100 g of cefaclor and 8.8 g of microcrystalline cellulose (Avicel® PH 102) were mixed in a planetary mixer and granulated with 35 ml of water according to the method described in example 1. After blending the granulate with the remaining part of the microcrystalline cellulose and the other excipients, tablets having a mean weight of 312 mg and a hardness of 4.3 kP were compressed. The disintegration time in water was 21.3 s.

Example 14

100 ml of an aqueous solution of 0.1 N hydrochloric acid was warmed in a beaker of 250 ml in a water bath of 37°C. A tablet according to the invention was put into the beaker. After 30 minutes the beaker was swung gently in order to disperse the particles. The appearance of the particles was assessed visually.

In this test it was observed that e.g. cefaclor has intrinsically sticking properties: a gel was formed and lumps could be observed. The tablets prepared according to examples 2-13 readily disintegrated to form a fine dispersion and no stickiness was observed at all.

## CLAIMS

1. Composition for oral administration comprising a cephalosporin antibiotic and one or more of an agent capable of reducing under wet conditions intrinsically sticking properties of the cephalosporin antibiotic optionally in admixture with pharmaceutically acceptable excipients.

2. Composition according to claim 1, characterised in that the agent is selected from the group consisting of sodium lauryl sulfate, cross-linked polyvinylpyrrolidone, sodium starch glycolate, bentonite, magnesium aluminium silicate, croscarmellose sodium and microcrystalline cellulose.

3. Composition according to claim 2, characterised in that the agent is microcrystalline cellulose.

4. Composition according to any one of claims 1-3, characterised in that the agent is present in an amount of up to 17 wt%, the percentage based on the weight of the cephalosporin antibiotic.

5. Composition according to claim 4, characterised in that the agent is present in an amount of < 10 wt%, the percentage based on the weight of the cephalosporin antibiotic.

6. Composition according to any one of claims 1-5, characterised in that the cephalosporin antibiotic is present in an amount of more than 83 wt%, the percentage based on the weight of the composition.

7. Composition according to any one of claims 1-6, characterised in that the cephalosporin antibiotic is cefaclor.

8. Composition according to any one of claims 1-7 characterised in that the cephalosporin antibiotic and the agent are present in granules, obtained by a wet granulation technique.

9. Composition according to any one of claims 1-8, characterised in that one or more extragranular disintegrants are present.

10. Composition according to claim 9, characterised in that the disintegrant is selected from the group consisting of cross-linked polyvinylpyrrolidone, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, polacrilin potassium and sodium starch glycolate.

11. Composition according to claim 10, characterised in that the disintegrant is cross-linked polyvinylpyrrolidone or low-substituted hydroxypropyl cellulose.

12. Use of an agent, selected from the group consisting of sodium lauryl sulfate, cross-linked polyvinylpyrrolidone, sodium starch glycolate, bentonite, magnesium aluminium silicate, croscarmellose sodium and microcrystalline cellulose, in a composition for oral administration, containing a cephalosporin antibiotic, for reducing under wet conditions intrinsically sticking properties of the cephalosporin antibiotic.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/06350

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/545 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
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[X] Further documents are listed in the continuation of box C.

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